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Cerebrovascular Disease Mortality after occupational Radiation Exposure among the UK National Registry for Radiation Workers Cohort

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Exposure to ionizing radiation can damage the cerebrovascular system, however there is uncertainty regarding the effects after chronic exposure to low doses of radiation, such as that experienced by the public and those occupationally exposed. This study uses data from the UK National Registry for Radiation Workers cohort to assess the association between low-dose exposure to external radiation and cerebrovascular disease (CeVD) mortality. Poisson regression was used to estimate the Excess Relative Risk of CeVD mortality per Sievert (ERR/Sv) of radiation exposure. Estimates were obtained for all CeVD combined, ischemic stroke, hemorrhagic stroke and other/ill-defined CeVD. Results were adjusted for attained age, calendar period, sex, employer, industrial category and employment length. 166,812 nuclear workers (3,665,413 person-years) were included. By the end of 2011, 23% were dead including 3,219 deaths with an underlying cause of CeVD. The ERR/Sv for all CeVD deaths was 0.57 (95% CI: 0.00, 1.31; p = 0.05). Increased CeVD mortality rates were observed after doses as low as 10–20 mSv. However, a linear-exponential model fit the data significantly better than a linear model (p = 0.02). In the sub-type analyses, no evidence of linear associations were observed, however the patterns of response appeared to differ and there was some suggestion of an increased risk of hemorrhagic stroke at lower doses. These results are broadly consistent with other occupational cohort studies and suggest external radiation exposure may increase CeVD risk at lower doses than current ICRP protection guidelines suggest. Exploration of factors driving the observed dose-response shape, the potential impact of the healthy worker survivor effect, and further studies of cohorts with data on other potential confounders would be valuable.

INTRODUCTION

Cerebrovascular disease (CeVD) is a leading cause of disability and mortality worldwide, accounting for 11% of global deaths in 2019 (1). CeVD encompasses a number of conditions that affect the vasculature of the brain, but the vast majority of deaths are due to stroke (2). CeVD was first listed as a health hazard of ionizing radiation exposure by the International Commission of Radiological Protection (ICRP) in 2012 after a review of evidence from occupational, medical and accidental exposures and it has been classified as a tissue reaction, with no observable increase in risk from exposures below 0.5 Gy (3). This threshold dose has been suggested primarily based on observations of survivors of the atomic bombs dropped on Hiroshima and Nagasaki in 1945, but it remains unclear whether extrapolation of these observations, where individuals received a single acute radiation dose, to populations chronically exposed to low doses of radiation, such as the public and those occupationally exposed, is appropriate.

There are a number of occupational cohorts in which the effects of chronic exposure have been explored; however, they have generally lacked statistical power, resulting in high imprecision in their risk estimates (4–8). Recent reviews by Little et al., including medical, environmental and occupational studies, calculated an overall significant excess relative risk of CeVD mortality, however they also identified substantial heterogeneity between current studies, with estimates varying over two orders of magnitude (9–11). While some variation in estimates of radiation related risk between studies may be expected due to differences between populations and their underlying risk, the considerable heterogeneity, combined with the fact that most studies have poor control of confounding for important CeVD risk factors such as hypertension, makes interpretation of these results difficult. Due to the number of CeVD deaths included, some of the strongest evidence regarding CeVD risk after low-dose exposure comes from INWORKS, the international pooled study of radiation workers from the UK, U.S. and France (12). The INWORKS study observed an excess relative risk (ERR) for CeVD of 0.50 per Sv of occupational external radiation exposure (90% CI: 0.12, 0.94), although there was

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considerable heterogeneity between the country specific estimates.

The current evidence suggests that there may be increased CeVD risk after exposure to low doses of external radiation, but the uncertainty on the current estimates means further investigation is required. Given the high background rate of CeVD in the population, even a small excess relative risk for external radiation exposure could lead to substantial numbers of excess cases.

The National Registry for Radiation Workers (NRRW), established in 1976 to examine health effects of long-term exposure to low doses of radiation, has previously reported little evidence of an association between radiation and CeVD (13, 14). This analysis, with an additional 10 years of follow-up and nearly double the number of CeVD deaths, explores the risks of CeVD within the cohort in more depth.

METHODS

Cohort Definition

Full details of the NRRW study have been published previously (15). In brief, the NRRW comprises individuals employed by participating UK organizations between 1955 and present day who have been monitored for occupational external radiation exposure and for whom individual dose records have been kept. The major organizations in the UK participating in the study are the Ministry of Defence (MoD), the Atomic Weapons Establishment (AWE), Rolls Royce and Associates (RRA), research councils including the Science and Technology Facilities Council (STFC), the Medical Research Council (MRC) and Public Health England (PHE) and sites formerly owned by the now dissolved British Nuclear Fuels Ltd (BNFL), the United Kingdom Atomic Energy Authority (UKAEA) and British Energy Generation (BE).

Three major analyses of the NRRW cohort have been undertaken to date looking at effects of radiation on cancer incidence and all causes of mortality (14–16). The third analysis, reported in 2009, included follow-up data up to the end of 2001. This analysis considers the same group of individuals that was included in the third analysis, but with an additional 10 years of follow-up (13, 14). These individuals were in employment between January 1, 1955 and December 31, 2001.

The final analysis included 166,812 workers. 1,241 (0.7%) individuals were excluded from the analysis due to insufficient personal or dose data or incomplete follow-up information.

Exposure to Ionizing Radiation

Approved Dosimetry Services (ADSs) provided individual annual records of occupational external radiation dose, quantified using readings from personal dosimeters. The doses are mostly associated with X-ray and gamma-ray exposure with a small component from beta particles and neutrons. As in previous analyses of the NRRW cohort, corrections were applied to dose estimates to ensure consistency across different types of dosimeters and practices used over time and by different organizations (15). An internal monitoring status indicator is held in the NRRW, indicating whether cohort members have been monitored for internal radiation exposure, but no internal dose measurements are held.

Cumulative dose, in Sieverts, was the main exposure in this analysis grouped as follows (in mSv): 0-, 10-, 20-, 50-, 100-, 200-, 300-, 500-, 700+). For categorical analyses, the mean dose was assigned.

Doses were lagged by 10 years to account for the anticipated delay between exposure and any increase in CeVD risk. Alternative lag periods were considered in the sensitivity analyses.

Follow-up and Ascertainment of causes of Death

The start of follow-up for each individual was defined as the later of January 1, 1955 or 10 years after the start of radiation work. Follow-up ended on the earliest of the December 31, 2011, an individual's death date, or when an individual emigrated or was otherwise lost to follow-up.

Mortality data including dates of death and causes of death, coded using the International Classification of Diseases (ICD), were provided to the study by NHS (National Health Service) Digital and the National Records of Scotland (NRS). Only underlying cause of death was considered in this analysis.

Analyses considered all CeVD combined (ICD 9: 4300-4389) and 3 main subtypes of CeVD: hemorrhagic stroke (4300-4329), ischemic stroke (4330-4359) and other/ill-defined CeVD (4360-4389).

Statistical Methods

Individuals were categorized by the following covariates derived from data provided by the ADSs to create a person year table for analysis:

- Calendar period: Time-varying variable categorized into 5-year groups.
- Attained age: Time-varying variable categorized into 5-year age band (16–44, 45–49, 50–54, ..., 90+). The categories were reduced for the CeVD sub-type analyses due to data sparsity (16–54, 55–59, 60–64, ..., 85+).
- Sex.
- Employment length: Time-varying variable, calculated from the start of employment recorded in the NRRW database, categorized into 5-year bands (0–4, 5–9, ..., 30+).
- Employer: Grouped as per previous analyses of the NRRW cohort for comparability, shown in Table 1. Individuals who were employed by more than one participating employer during the study period (4%), were assigned to their first employer. Due to data sparsity, for the CeVD sub-type analyses a smaller number of groupings were used.
- Industrial category: As classified by employers (industrial or non-industrial); a crude proxy for socio-economic status, with industrial workers broadly being of lower socio-economic status than non-industrial workers. Industrial category was unknown in for 2,189 individuals (1.3%). Based on their other characteristics (particularly employer and radiation dose received), these individuals were grouped with the non-industrial individuals for the main analyses. Alternative grouping was explored in the sensitivity analyses.
- Age at start of employment: Calculated at the employment start date recorded in the NRRW database (16–29, 30–39, 40–49, 50+).
- Internal radiation monitoring status: Data on internal doses are not currently held in the NRRW, however a binary variable is held indicating whether individuals have been monitored for intakes of radioactive materials (primarily uranium, plutonium and tritium). This provides an indication of whether an individual may have been exposed to internal radiation, however some employers are known to widely monitor for internal radiation exposures even if the risk of exposure is negligible. This variable was therefore only considered in the sensitivity analyses. The majority of those monitored for internal radiation exposure were employees of the ex-BNFL or ex-UKAEA sites.

Poisson regression models were used to calculate the ERR of CeVD mortality per Sv of occupational radiation exposure and 95% likelihood confidence intervals, for all CeVD, ischemic stroke, hemorrhagic stroke and other/ill-defined CeVD. Models considered in this analysis were of the following form:

$$Overall\ Risk = Background\ Risk * (1 + \mathrm{ERR}(d))$$

Where d is radiation dose and background risk include adjustment for confounders. The main analyses were fully stratified by calendar

TABLE 1
Characteristics of the Study Cohort

	Number of individuals[a] n = 166,812 (%)	Total pyar n = 3,665,413 (%)	Median dose (mSv) (IQR)	CeVD deaths n = 3,219	Incidence rate per 10,000 pyar (95% CI)	SMR (95% CI)
	166,812	3,665,413	3.1 (0.3, 16)	3,219	8.8 (8.5, 9.1)	87 (84, 90)
Radiation dose (mSv)						
0-	114,442 (68)	2,498,741 (68)	0.9 (0.0, 3.3)	1,555	6.2 (5.9, 6.5)	80 (76, 84)
10–	15,829 (9.5)	365,696 (10)	14 (12, 17)	423	12 (11, 13)	89 (81, 98)
20–	17,622 (11)	399,638 (11)	31 (25, 39)	536	13 (12, 15)	91 (84, 99)
50–	9,206 (5.5)	199,283 (5.4)	68 (58, 82)	298	15 (13, 17)	94 (84, 106)
100–	5,524 (3.3)	118,978 (3.2)	134 (115, 161)	213	18 (16, 20)	107 (93, 122)
200–	1,926 (1.2)	40,045 (1.1)	239 (217, 266)	79	20 (16, 25)	106 (85, 133)
300–	1,485 (0.9)	29,864 (0.8)	375 (334, 427)	65	22 (17, 28)	92 (72, 117)
500–	504 (0.3)	8,709 (0.2)	573 (533, 628)	34	39 (28, 55)	137 (98, 192)
700+	274 (0.2)	4,460 (0.1)	826 (752, 953)	16	36 (22, 59)	99 (61, 162)
Attained age (years)						
26–44	19,862 (12)	1,185,059 (32)	1.3 (0.1, 6.9)	43	0.4 (0.3, 0.5)	78 (58, 106)
45–49	16,835 (10)	509,205 (14)	2.6 (0.3, 13)	59	1.2 (0.9, 1.5)	73 (56, 94)
50–54	20,137 (12)	472,871 (13)	3.4 (0.4, 17)	100	2.1 (1.7, 2.5)	77 (63, 93)
55–59	18,989 (11)	430,022 (12)	4.2 (0.5, 21)	143	3.3 (2.8, 3.9)	71 (61, 84)
60–64	21,340 (13)	367,991 (10)	5.1 (0.6, 25)	228	6.2 (5.4, 7.1)	73 (65, 84)
65–69	20,245 (12)	282,329 (7.7)	6.7 (1.0, 31)	372	13 (12, 15)	81 (74, 90)
70–74	17,252 (10)	200,516 (5.5)	8.5 (1.4, 37)	569	28 (26, 31)	92 (84, 100)
75–79	14,579 (8.7)	122,367 (3.3)	10 (1.8, 41)	649	53 (49, 57)	93 (86, 101)
80–84	10,251 (6.2)	60,487 (1.7)	11 (2.1, 41)	589	97 (90, 106)	97 (89, 105)
85–89	5,296 (3.2)	21,669 (0.6)	10 (2.2, 38)	333	154 (138, 171)	85 (78, 93)
90+	2,026 (1.2)	5,897 (0.2)	9.1 (1.9, 29)	134	227 (192, 269)	
Calendar period						
1955–1969	1,014 (0.6)	104,954 (2.9)	5.6 (0.8, 18)	77	7.3 (5.9, 9.2)	88 (70, 110)
1970–1974	1,511 (0.9)	142,841 (3.9)	5.8 (1.3, 21)	107	7.5 (6.2, 9.1)	83 (68, 100)
1975–1979	2,476 (1.5)	216,456 (5.9)	5.3 (0.8, 21)	206	9.5 (8.3, 11)	99 (87, 114)
1980–1984	3,411 (2.0)	303,936 (8.3)	4.2 (0.4, 20)	301	9.9 (8.8, 11)	105 (94, 118)
1985–1989	4,140 (2.5)	383,791 (10)	3.5 (0.3, 19)	328	8.5 (7.7, 9.5)	86 (77, 96)
1990–1994	5,299 (3.2)	475,450 (13)	3.2 (0.3, 17)	397	8.3 (7.6, 9.2)	85 (77, 93)
1995–1999	6,394 (3.8)	548,349 (15)	2.9 (0.3, 16)	438	8.0 (7.3, 8.8)	79 (72, 87)
2000–2004	8,145 (4.9)	606,155 (17)	2.4 (0.3, 14)	600	9.9 (9.1, 11)	92 (85, 99)
2005–2009	6,970 (4.2)	631,600 (17)	2.1 (0.3, 12)	561	8.9 (8.2, 9.6)	83 (77, 90)
2010 onwards	127,452 (76)	251,880 (6.9)	2.0 (0.3, 11)	204	8.1 (7.1, 9.3)	76 (67, 88)
Sex						
Male	150,390 (90)	3,345,646 (91)	3.4 (0.4, 18)	3,046	9.1 (8.8, 9.4)	87 (84, 90)
Female	16,422 (10)	319,767 (8.7)	1.3 (0.2, 5.1)	173	5.4 (4.7, 6.3)	83 (72, 97)
Employer/facility of employment						
UKAEA Dounreay	6,308 (3.8)	161,349 (4.4)	10 (2.5, 35)	164	10 (8.7, 12)	111 (95, 129)
UKAEA Winfrith	3,597 (2.2)	91,019 (2.5)	6.9 (1.6, 33)	90	9.9 (8.0, 12)	85 (69, 105)
UKAEA Harwell	13,837 (8.3)	399,988 (11)	8.2 (2.2, 26)	506	13 (12, 14)	77 (71, 84)
UKAEA Risley	2,534 (1.5)	65,714 (1.8)	0.9 (0.2, 3.8)	87	13 (11, 16)	82 (66, 101)
BNFL Sellafield	19,919 (12)	450,005 (12)	23 (5.1, 82)	479	11 (9.7, 12)	107 (98, 117)
BNFL Chapelcross	1,925 (1.2)	46,870 (1.3)	27 (7.2, 78)	69	15 (12, 19)	115 (91, 146)
BNFL Other	16,766 (10)	403,484 (11)	4.4 (0.9, 14)	614	15 (14, 16)	98 (91, 107)
AWE	14,166 (8.5)	294,518 (8.0)	18 (0.4, 6.1)	331	11 (10, 13)	81 (73, 90)
MoD	62,240 (37)	1,218,917 (33)	0.4 (0.0, 3.0)	465	3.8 (3.5, 4.2)	72 (66, 79)
BE England and Wales	12,712 (7.6)	311,484 (8.5)	7.1 (1.6, 22)	284	9.1 (8.1, 10)	84 (74, 94)
GE Healthcare	3,772 (2.3)	59,622 (1.6)	2.3 (0.1, 16)	27	4.5 (3.1, 6.6)	69 (47, 100)
STFC/MRC/PHE	2,885 (1.7)	63,824 (1.7)	2.7 (0.4, 12)	47	7.4 (5.5, 9.8)	75 (56, 100)
RRA + Other	3,138 (1.9)	54,010 (1.5)	0.7 (0.0, 8.9)	19	3.5 (2.2, 5.5)	50 (32, 78)
BE Scotland	3,013 (1.8)	44,609 (1.2)	6.0 (0.7, 29)	37	8.3 (6.0, 11)	120 (87, 165)
Industrial category						
Industrial	94,342 (57)	2,016,380 (55)	2.9 (0.3, 16)	2,072	10 (9.8, 11)	97 (93, 102)
Non-industrial	70,281 (42)	1,610,104 (44)	3.4 (0.4, 16)	1,104	6.9 (6.5, 7.3)	72 (68, 76)
Unknown	2,189 (1.3)	38,929 (1.1)	0.2 (0.0, 2.5)	43	11 (8.2, 15)	91 (67, 123)

Continued on next page

TABLE 1
Continued.

	Number of individuals[a] n = 166,812 (%)	Total pyar n = 3,665,413 (%)	Median dose (mSv) (IQR)	CeVD deaths n = 3,219	Incidence rate per 10,000 pyar (95% CI)	SMR (95% CI)
Employment length (years)						
0–4	70,040 (42)	1,469,855 (40)	0.9 (0.1, 4.1)	1,088	7.4 (7.0, 7.9)	87 (82, 92)
5–9	30,127 (18)	585,363 (16)	2.8 (0.4, 12)	563	9.6 (8.9, 10)	91 (84, 99)
10–14	21,431 (13)	607,798 (17)	3.0 (0.4, 13)	495	8.1 (7.5, 8.9)	90 (82, 98)
15–19	15,689 (9.4)	401,907 (11)	10 (2.5, 31)	376	9.4 (8.5, 10)	88 (80, 97)
20–24	12,654 (7.6)	274,779 (7.5)	19 (5.6, 55)	280	10 (9.1, 11)	88 (78, 99)
25–29	8,225 (4.9)	170,098 (4.6)	31 (11, 85)	201	12 (10, 14)	80 (70, 92)
30+	8,646 (5.2)	155,614 (4.2)	52 (20, 136)	216	14 (12, 16)	74 (65, 84)
Age at start of employment (years)						
16–29	102,844 (62)	2,404,055 (66)	2.9 (0.3, 15)	622	2.6 (2.4, 2.8)	77 (71, 83)
30–39	35,190 (21)	777,657 (21)	3.7 (0.4, 20)	839	11 (10, 12)	84 (78, 89)
40–49	19,008 (11)	353,191 (9.6)	3.5 (0.4, 17)	975	28 (26, 29)	93 (88, 99)
50+	9,770 (5.9)	130,510 (3.6)	2.3 (0.3, 9.4)	783	60 (56, 64)	92 (86, 99)
Monitored for internal radiation						
No	125,594 (75)	2,707,255 (74)	1.6 (0.1, 8.3)	2,131	7.9 (7.5, 8.2)	83 (80, 87)
Yes	41,218 (25)	958,158 (26)	15 (3.8, 52)	1,088	11 (11, 12)	95 (89, 100)

Abbreviations: pyar, person-years at risk; mSv, millisieverts; IQR, interquartile range; CeVD, cerebrovascular disease; CI, confidence interval; SMR, standardized mortality ratio.

[a] For time-varying variables (radiation dose, attained age, calendar period, employment length), individuals are counted in their category at the end of follow-up.

period, attained age, sex, employment length, first employer and industrial category (including all interaction terms). Due to sparsity of data, reduced groupings were used for attained age and first employer for the sub-type analyses. Potential effect modification by attained age, age at start of employment, industrial category, length of employment and internal exposure monitoring was examined using likelihood ratio tests.

The shape of the dose response was further explored by fitting categorical, linear-exponential ($ERR(d) = \beta_1 d^* \exp(\beta_2 d)$), quadratic ($ERR(d) = \beta d^2$) and linear-quadratic ($ERR(d) = \beta_1 d + \beta_2 d^2$) models. Likelihood ratio tests, where models were nested, and Akaike Information Criteria were used to compare goodness of fit (17).

The following sensitivity analyses were conducted:

1. Adding adjustment for internal exposure monitoring to the full model.
2. Recategorizing industrial category such that unknown individuals were grouped with industrial workers instead of non-industrial.
3. Using the reduced covariate groupings used in the sub-type analyses.
4. Censoring individuals at the age of 85 years (this is often done in other analyses as there is concern about the quality of underlying cause of death data recorded in older individuals and competing causes of death).
5. Using different lag periods: 5, 15 and 20 years.
6. Restricting the maximum dose included in the analysis: 1000, 500, 200 mSv.

To explore the possibility of the ERR estimates being confounded by smoking, the fully adjusted model from the main analysis was fitted to chronic obstructive pulmonary disease (COPD) deaths.

As well as comparing risk of CeVD mortality within the NRRW cohort, the CeVD mortality experience of the cohort was compared to the general population of England and Wales stratified by age group, calendar period and sex. The 20th and 21st century mortality files published by the Office for National Statistics (ONS) were used to derive CeVD deaths rates for the general population and calculate standardized mortality ratios (SMRs) and 95% CIs for each variable and overall (18, 19).

All risk modelling was performed using the AMFIT module of Epicure 2.0 (Risk Sciences International) (20).

RESULTS

Table 1 shows a full distribution of characteristics of the study cohort. Over a third of the individuals were employees of the MoD and 39% were from sites previously owned by BNFL or UKAEA. The cohort was predominantly male (90%) and most had started radiation work before the age of 30 (62%).

The total cumulative occupational radiation dose received by members of the cohort ranged from 0 to 1.9 Sv, however the distribution of doses was highly skewed, with the majority of the workers only exposed to very low doses. The median dose was 3.1 mSv (IQR: 0.3, 16) and 94% of individuals received a total cumulative dose of less than 100 mSv.

As would be expected, attained age and employment length both increased with radiation exposure. Employees from ex-BNFL sites received the highest average doses and comprise 67% of individuals with a lifetime dose of 300 mSv or more. Amongst those with a total dose less than 10 mSv, 47% were employed by the MoD. Internal monitoring is also strongly skewed with dose, with only 15% of those in the lowest dose group monitored compared to 81% of those with a total dose of at least 300 mSv.

Individuals were followed up for a mean of 22 years (excluding the initial 10-year lag), resulting in a total of 3,665,413 person-years being included in the final analyses. By the end of follow-up, 23% of the cohort had died, with

TABLE 2
Distribution of Cerebrovascular Disease (CeVD) and Chronic Obstructive Pulmonary Disease (COPD) as Underlying Cause of Death

Radiation dose (mSv)	Total	All CeVD	Ischemic stroke	Hemorrhagic stroke	Ill-defined/other CeVD	COPD
0	20,376	1,555	215	359	981	892
10	4,690	423	45	76	302	215
20	5,883	536	71	95	370	287
50	3,384	298	36	66	196	133
100	2,236	213	30	40	143	95
200	889	79	8	17	54	38
300	772	65	7	4	54	26
500	315	34	5	8	21	13
700+	183	16	5	1	10	8
Total	38,728	3,219	422	666	2,131	1,707

3,219 deaths attributed to CeVD (Table 2). Only 2.1% of individuals were lost to follow-up.

Association between Radiation Exposure and CeVD Mortality

After adjusting for calendar period, attained age, sex, employment length, first employer and industrial category, there was some evidence of a linear association between external radiation exposure and CeVD mortality ($p = 0.05$). The estimated ERR/Sv was 0.57 (95% CI: 0.00, 1.31) (Fig. 1a).

The categorical analysis suggests a strong increase in risk at very low doses (<200 mSv), followed by a plateauing of risk, and even a potential decrease at higher doses (Fig. 1a). This is also reflected by the linear-exponential model which was the best fitting model out of those tested and fits significantly better than the linear model ($p = 0.016$) (Fig. 1b).

Splitting CeVD into subtypes, different patterns are observed (Fig. 2). There is no evidence of a linear association between ischemic strokes and radiation exposure ($p = 0.16$) and all the categorical ERR estimates are grouped around 0. There is a suggestion of an increase in risk for hemorrhagic stroke at lower doses, with some evidence of increased rate of CeVD among those exposed to 50–300 mSv. However, there is no increase in risk among those exposed to greater than 300 mSv (ERR = 0.06, $p > 0.5$) and no overall evidence of a linear association ($p = 0.15$). The ill-defined strokes and other CeVD grouping displays a steady ERR of around 0.3 among all exposure groups; there is little evidence of a linear association ($p = 0.11$).

There was no evidence of an interaction between radiation exposure and attained age ($p = 0.22$), industrial category ($p > 0.5$), employment length ($p > 0.5$) or age at the start of employment ($p > 0.5$) (Table 3). However, higher risks were observed ($p = 0.03$) among those who had not been monitored for internal radiation exposure (ERR/Sv: 1.63; 95% CI: 0.34, 2.93) compared to those who had been monitored (ERR/Sv: 0.36; 95% CI: –0.22, 0.94). This heterogeneity is observed across the full dose range and excluding each employer group in turn has limited effect. Those monitored for internal exposure are more likely to have started working earlier in the sites' history and been employed in radiation work for longer, resulting in considerably higher cumulative external doses (median dose of 15 mSv vs. 1.6 mSv for those not monitored).

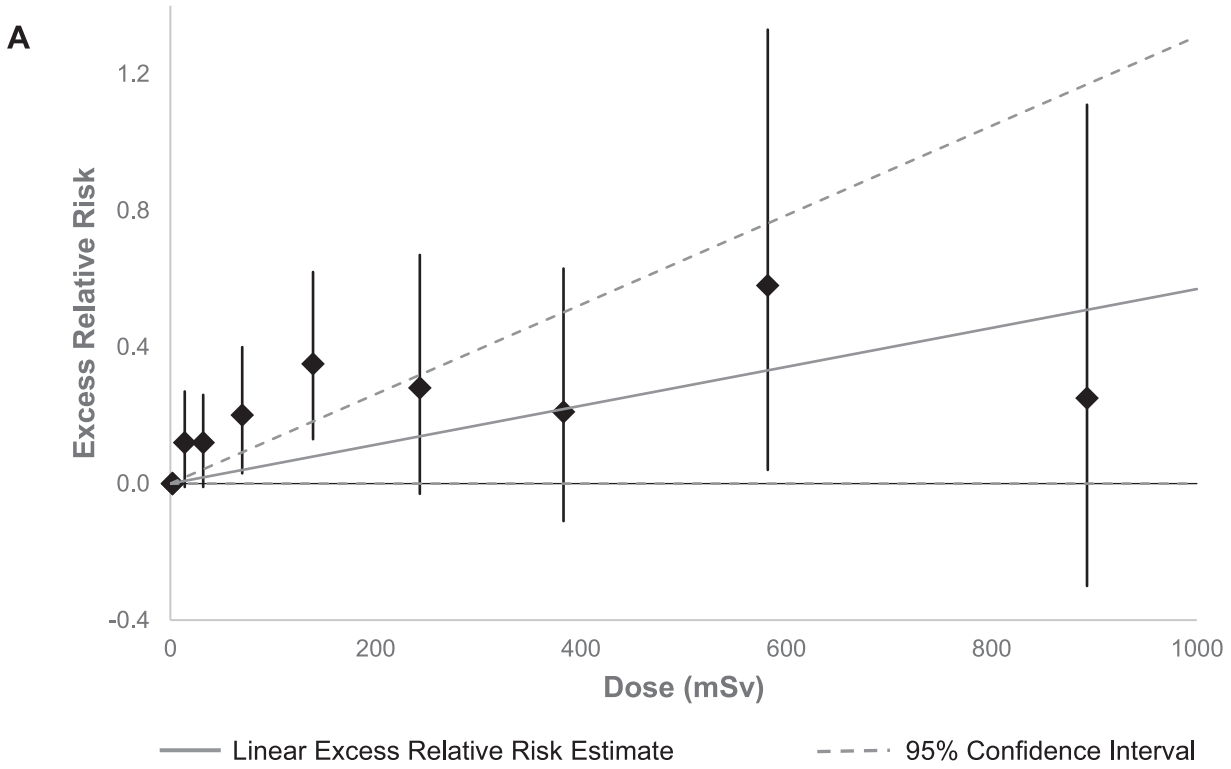
Most of the sensitivity analyses had little impact on the risk estimate (Table 4), however, using the reduced groupings for attained age and employer as used in the subgroup analyses increased the risk estimate (ERR/Sv: 0.71). There was no evidence of association between radiation exposure and CeVD mortality when the lag period was reduced to 5 years, however, increasing the lag period had limited effect on the ERR estimate; all point estimates were consistent although the statistical power was reduced. Unsurprisingly given the shape of the observed dose-response pattern, progressively restricting the maximum

TABLE 3
Results of Interaction Tests

	ERR/Sv	95% CI	p value
Attained age (years)			
26–59	–0.15	–2.19, 1.88	0.22
60–69	–0.07	–1.36, 1.23	
70–79	1.38	0.20, 2.56	
80+	–0.01	–0.76, 0.74	
Industrial category			
Industrial	0.65	–0.14, 1.45	>0.5
Non-industrial	0.40	–0.53, 1.32	
Employment length (years)			
0–9	1.85	–0.46, 4.16	>0.5
10–19	0.15	–0.085, 1.15	
20–29	0.48	–0.44, 1.40	
30+	0.85	–0.60, 2.30	
Age at start of employment (years)			
16–29	0.59	–0.40, 1.58	>0.5
30–39	0.78	–0.14, 1.69	
40–49	0.39	–0.57, 1.35	
50+	0.37	–1.37, 2.11	
Monitored for internal radiation			
No	1.63	0.34, 2.93	0.03
Yes	0.36	–0.22, 0.94	

Abbreviations: ERR, excess relative risk; Sv, Sievert; CI, confidence interval.

Note. Adjusted for attained age, calendar period, sex, employer group, industrial category and employment length.



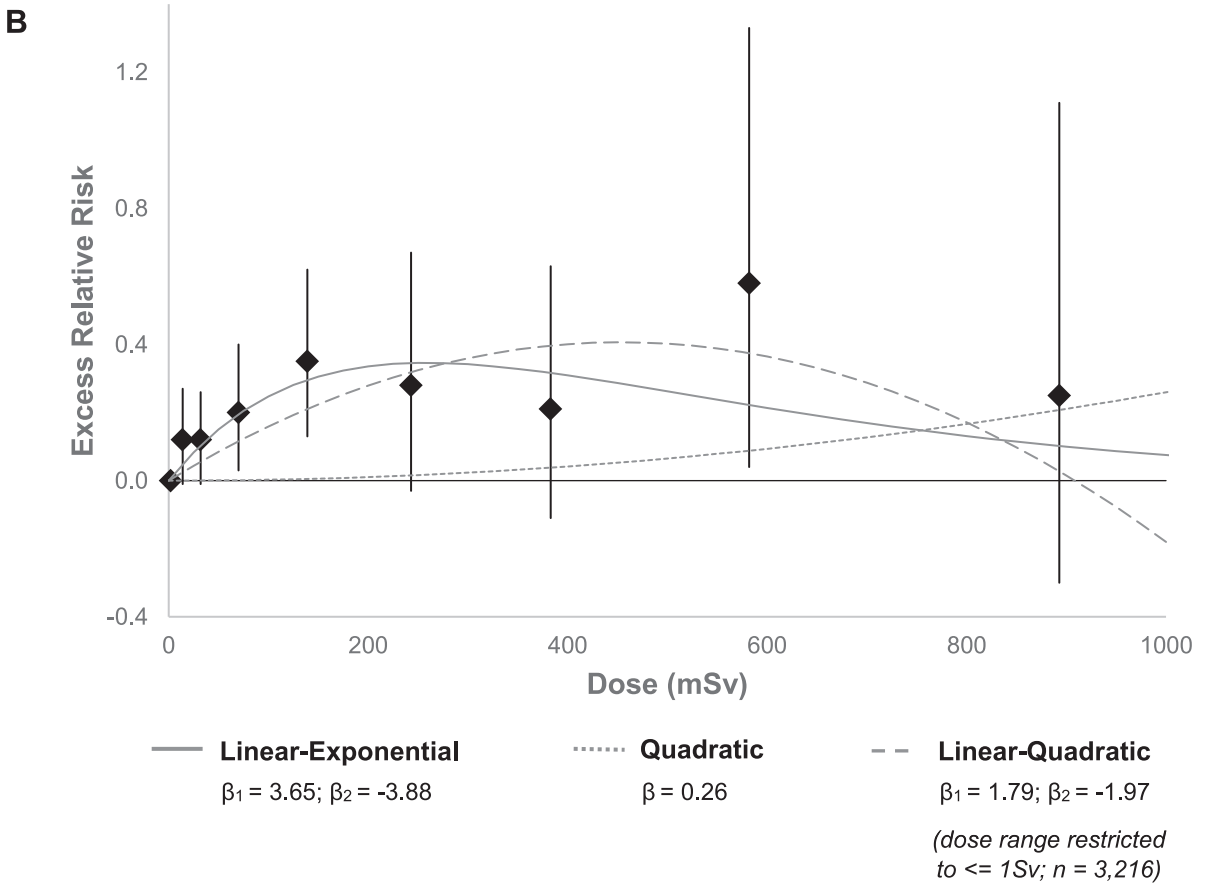


FIG. 1. Association between external ionizing radiation exposure and risk of mortality from cerebrovascular disease (n = 3,219). Panel A: Linear model. Excess relative risk/Sv: 0.57; 95% CI: 0.00, 1.31. Panel B: Alternate models. Adjusted for calendar period, attained age, sex, employment length, first employer and industrial category.

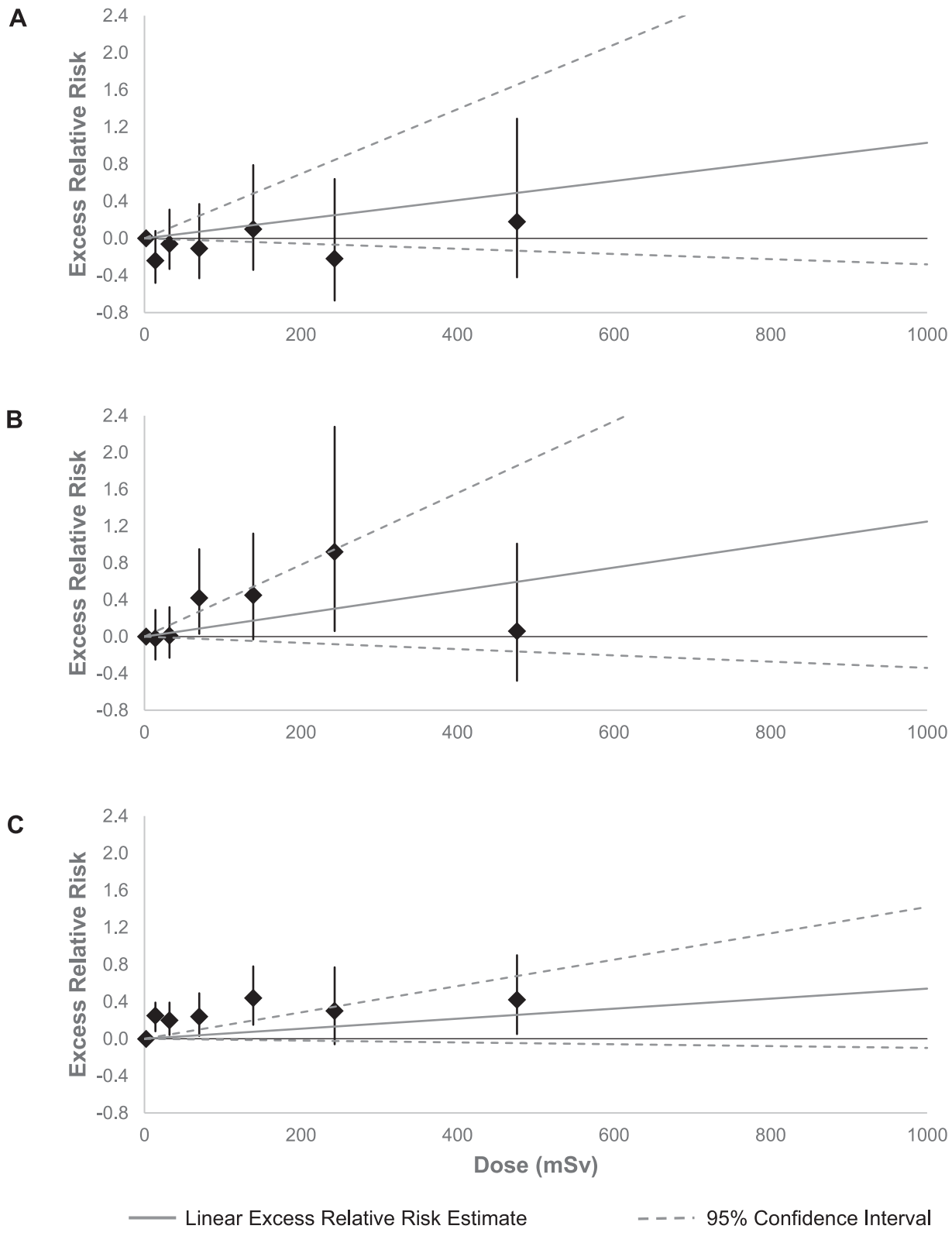


FIG. 2. Association between external ionizing radiation exposure and risk of mortality from different types of cerebrovascular disease. Panel A: Ischemic stroke (n = 422), ERR/Sv: 1.03; 95% CI: –0.28, 3.48. Panel B: Hemorrhagic stroke (n = 666), ERR/Sv: 1.06; 95% CI: –0.52, 2.01. Panel C: Ill-defined and other CeVD (n = 2,131), ERR/Sv: 0.54; 95% CI: –0.10, 1.42. Adjusted for calendar period, attained age, sex, employment length, first employer and industrial category.

TABLE 4
Results of Sensitivity Analyses

	Number of CeVD deaths	ERR/Sv	95% CI	p value
Main analysis	3,219	0.57	0.00, 1.31	0.05
Adding adjustment for internal monitoring	3,219	0.56	–0.088, 1.21	0.07
Recategorizing industrial category	3,219	0.58	0.01, 1.33	0.05
Using reduced covariate groupings	3,219	0.71	0.13, 1.47	0.014
Censoring at 85	2,752	0.60	–0.02, 1.43	0.06
5-year lag[a]	2,809	0.33	–0.19, 1.03	0.24
15-year lag	3,021	0.57	–0.026, 1.36	0.06
20-year lag	2,716	0.63	–0.030, 1.53	0.06
Dose range: 0–1,000 mSv	3,215	0.63	0.018, 1.42	0.04
Dose range: 0–500 mSv	3,169	2.39	–0.22, 5.48	0.07
Dose range: 0–200 mSv	3,025	3.87	–0.88, 9.51	0.12

Abbreviations: ERR, excess relative risk; Sv, Sievert; CI, confidence interval.
Note. Adjusted for attained age, calendar period, sex, employer group, industrial category and employment length.
[a] Follow-up censored on December 31, 2006.

dose included in the analysis resulted in an increasing ERR estimate, but this is associated with high uncertainty.

Chronic Obstructive Pulmonary Disease

There were 1,707 deaths with COPD as the underlying cause amongst the cohort (4.7 deaths per 10,000 person-years at risk). No evidence of an association between radiation exposure and COPD mortality was found ($p > 0.5$) (Fig. 3).

Standardized Mortality Ratios

The observed rate of CeVD mortality in the NRRW cohort was 13% lower than the population of England and Wales, adjusting for age, sex and calendar period (95% CI: 10, 16). SMRs for each variable are given in Table 1. One of the biggest differences in SMR observed was between industrial and non-industrial workers. Industrial workers had a similar rate of CeVD morality to the general population (SMR: 97, 95% CI: 93,102), while the rate in non-industrial workers was 28% lower (95% CI: 24, 32).

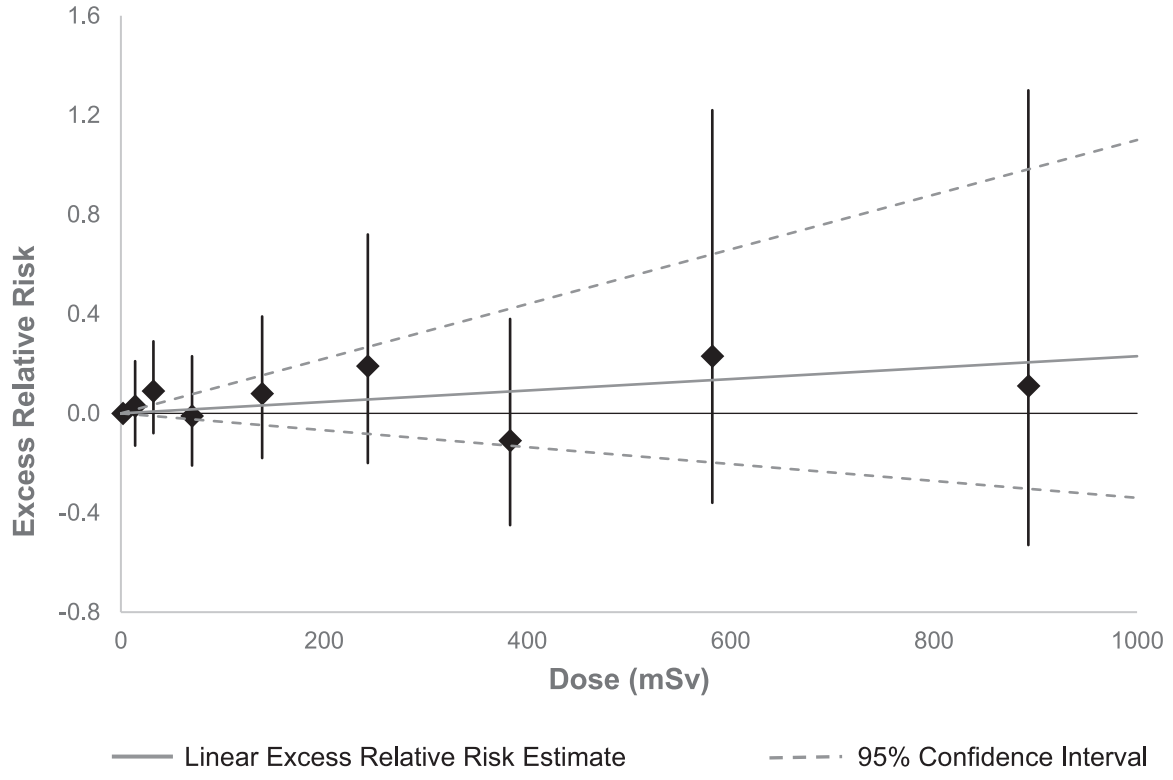


FIG. 3. Association between external ionizing radiation exposure and risk of mortality from chronic obstructive pulmonary disease (n = 1,707). Excess relative risk/Sv: 0.23; 95% CI: –0.34, 1.10. Adjusted for calendar period, attained age, sex, employment length, first employer and industrial category.

DISCUSSION

The cohort displayed a strong healthy worker effect (HWE), with a 13% lower risk of mortality from CeVD than the general population of England and Wales, adjusted for age, sex and calendar period (95% CI: 10, 16). This is unsurprising as the HWE is typically observed in occupational cohorts and arises because the occupational group must be healthy enough to be employed and so have a lower risk of mortality than the general population (21). The health of radiation workers is also routinely monitored by their employers and they must be sufficiently healthy to remain in radiation work. This also increases the chance of picking up health problems early. The comparison of workers with differing doses within the cohort is therefore more useful for assessing whether radiation exposure increases the risk of CeVD mortality.

The analysis found some evidence that the rate of CeVD mortality increased linearly with increasing exposure to external ionizing radiation after adjusting for age, sex, calendar period, employer group, length of employment and industrial category (ERR/Sv: 0.57; 95% CI: 0.00, 1.31; $p = 0.05$). However, a linear-exponential model was a better fit to the observed data ($p = 0.016$). A strong increase in risk was observed at very low doses, followed by a plateau, and even slight decrease, for doses above 200 mSv (Fig. 1).

However, a linear-exponential relationship between external radiation exposure and CeVD risk is unlikely to be biologically plausible. A potential explanation for the observed relationship is the healthy worker survivor effect (HWSE), an extension of the HWE. The HWSE occurs because less healthy individuals are more likely to leave employment than more healthy workers. This can result in negative confounding as workers who are healthier, and therefore have lower mortality rates, stay in employment longer and accumulate higher doses (22, 23).

To control for the HWSE, duration of employment was adjusted for in the main analysis. Inclusion of duration of employment resulted in an increase in the risk estimates, indicating that the HWSE is likely to be an important factor in the analysis of CeVD risks in this study. Unfortunately, the actual potential impact of the HWSE on risk estimates is not directly measurable and duration of employment is only a surrogate measure. Residual confounding is therefore likely and may be a potential explanation for the linear-exponential dose response observed. G-methods are an alternative method which could potentially be employed to control for the HWSE, but were beyond the scope of this analysis (24).

A biological mechanism for the effects of radiation on CeVD has not yet been established. Evidence from humans and experimental studies has shown that inflammatory markers are upregulated after exposure to radiation (0.5–5 Sv), and remain upregulated for a long time postirradiation, causing damage to the circulatory system (25, 26). However, at lower doses, exposure may trigger an anti-inflammatory response in inflamed tissues (26, 27). Recent research has identified a potential alternative mechanism of damage to the circulatory system at very low doses (28). Endothelial cells with radiation-induced DNA damage have been shown to become senescent and persistent changes to gene expression result in the cells becoming adhesive to monocytes. After adhesion to endothelial cells, monocytes may infiltrate vessel walls, initiating development of atherosclerotic plaques which can lead to circulatory and cerebrovascular disease.

The results of the sub-type analyses here do not provide support to this hypothesis, however, as no increase in risk associated with radiation dose was observed for ischemic stroke, which is often caused by atherosclerosis (29). Instead, some increase in risk of hemorrhagic stroke, which usually results from hypertension and weakened blood vessels, was suggested at lower doses (29). The variation in the relationship between ionizing radiation and different sub-types of cerebrovascular disease observed in this study may be an indication that there are different mechanisms of effect or that the strength of the HWSE differs across the subtypes of the disease. Hemorrhagic stroke risk in particular appears to display a strong reduction in risk at doses above 300 mSv. However, due to the far smaller number of events used for these analyses, full adjustment not being possible due to data sparsity and an increased risk of outcome misclassification, these results should be treated cautiously.

The ERR/Sv estimated here for CeVD mortality using a linear no-threshold model, is broadly consistent with that estimated in several other occupational cohort studies (4–6, 8, 12) but is substantially higher than the estimate from the Life Span Study (LSS) which found a risk estimate of 0.09 per Gy (95% CI: 0.01–0.17) (30). The LSS results further suggested that there was a threshold of effect of 500 mSv, below which exposure had no impact on CeVD (30). An increase in risk was observed at far lower doses in this study. The risk estimate is also higher than that from the Russian Federation Mayak worker cohort, which reported no evidence of increased mortality from CeVD although there was evidence of increased incidence (7).

The radiation exposures in the LSS and Mayak cohorts are very different from the low-dose, chronic exposure experienced by the NRRW cohort. Individuals in the LSS were exposed to a single acute, comparatively high dose while the Mayak Worker cohort, comprised of individuals who worked at the Mayak Production Association plants in the Southern Urals of Russia, was chronically exposed but to far higher doses than in the NRRW cohort with a mean dose of 620 mSv compared to 24 mSv. Further, the baseline rates of disease within the cohorts differed considerably – CeVD accounted for a far higher proportion of deaths in the LSS study than within the NRRW and the overall rate of CeVD was also considerably greater in the Mayak cohort. This difference is likely at least partly due to the age of the cohorts. Both the LSS and Mayak cohorts are more mature

than the NRRW; significantly greater proportions of the cohorts are dead. Further, the LSS cohort comprises individuals exposed over a whole range of ages whereas the NRRW only includes those exposed during working ages. Given these significant differences in exposure and baseline risk, extrapolation of the results from the LSS or Mayak cohorts to Western populations chronically exposed to low doses should be treated cautiously.

A major limitation of this study is lack of information on other risk factors for CeVD which may have a confounding effect on the association between radiation exposure and CeVD mortality. This is particularly important since the magnitude of any risk after exposure would be small compared to that from other well-known major CeVD risk factors. This analysis found no evidence of an association between radiation exposure and COPD which implies that there is no association between radiation exposure and smoking as around 90% of COPD cases are directly caused by smoking (31). This gives confidence that the relationship observed between radiation and CeVD mortality is not being strongly confounded by smoking, but factors such as hypertension or other occupational exposures could be still confounding the association. For example, an increased incidence and mortality from pleural cancer, which is the predominant type of mesothelial cancer (32), has previously been observed in the NRRW cohort (33). This could indicate that there may have been increased asbestos exposure among those exposed to the highest levels of radiation. There is also some evidence to suggest that asbestos exposure is associated with an increased risk of stroke, meaning asbestos exposure could be leading to an overestimation of the association between radiation and CeVD mortality in this study, although this effect is likely to be small (34).

The effect of potential confounders was recently investigated by de Vocht et al. in a subset of the NRRW cohort using a nested case-control study of BNFL workers (35, 36). The analyses found that adjusting for possible confounders, including smoking, blood pressure and body mass had little effect on the association observed between external radiation and ischemic heart disease. Further, the analyses suggested that any unmeasured confounder would have to be highly correlated with radiation exposure to meaningfully bias the observed association (36).

The results suggest that there may be a difference in CeVD risk associated with external radiation exposure between those who have been monitored for internal exposure and those who have not ($p = 0.03$). Heterogeneity was observed across the dose range and is not explainable by any single employer group. Interpretation of the observed heterogeneity is difficult without further details on the internal doses. Similar results have, however, previously been observed for both cancer and non-cancer outcomes in the BNFL worker cohort and it has been suggested that this may point to unaccounted confounding (8, 37). Work is currently being undertaken to add internal monitoring data to parts of the NRRW cohort which will allow further analysis of this.

The classification of the cases was based on underlying cause of death recorded in the NHS and NRS death registers, so the level of misclassification is anticipated to be low and unlikely to introduce significant bias. Sensitivity and specificity of the cause of death records are likely to be lower when considering narrower ICD ranges in the subtype analyses and many deaths are recorded as ill-defined. Any misclassification is not expected to be differential with respect to radiation exposure, but the lower accuracy may have led to some underestimation of relative risk in the subtype analyses.

Despite its limitations, this is the largest analysis of CeVD in a single occupationally exposed cohort to date, and so has greater power than previous studies. The study also has a very high coverage of the eligible population; less than 1% of those eligible opted-out. Data audits have been conducted with participating organizations to ensure all eligible individuals have been recorded. Further, high follow-up rates were achieved because the study is records based and does not require contact with the individuals. The risk of selection bias is therefore low. By the end of the analysis period, only 23% of the cohort were dead. The NRRW cohort continues to be expanded and as more members, further years of follow-up, and additional deaths are added, the power will increase significantly allowing risk estimates to be calculated with greater precision. This will be especially important for further exploration of sub-types of strokes where the numbers are currently limited.

CONCLUSION

This analysis has found some evidence that occupational exposure to low doses of radiation is associated with an increased risk of mortality from CeVD. Based largely on the results from the LSS, the ICRP currently suggest that the smallest exposure which may result in an increased risk of cerebrovascular diseases is 500 mSv (3). However, this study supports evidence that radiation may have a significant effect on CeVD at lower doses. Although the observed excess relative risk of 57% per Sievert, is relatively high, most individuals, including those exposed to radiation occupationally, are exposed to very low doses of radiation. In this cohort, the average lifetime occupational exposure was only 3.1 mSv which equates to an increase in risk of mortality from CeVD of just 0.17%. Nevertheless, given the high background rate of CeVD, even a small additional risk from radiation could lead to substantial excess cases and might therefore be an important public health concern. A major limitation of this study, and nearly all occupational studies to date, is lack of data on possible lifestyle confounding factors. Work is currently being undertaken to investigate options for obtaining additional data such as BMI, blood pressure, smoking and alcohol consumption history for at least part of the NRRW cohort,

which should provide valuable information. Another important area for further research is the Healthy Worker Survivor Effect and how it can be accounted for in occupational cohorts to avoid biased risk estimates.

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